Radiocontrast nephropathy *(renal protection)*

Papendorf D
Private Anaesthetist and Intensivist; Part-time lecturer Wits University

Correspondence to: Dr David Papendorf, e-mail: davidpa@iafrica.com

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INTRODUCTION

Renal protection has remained a highly topical subject for years. There are numerous medical interventions (both diagnostic and therapeutic) which put the kidney at risk. Many protective strategies have been tested and most have proven to be of no benefit. The focus of any prophylactic strategy remains *adequate hydration*. This presents new challenges to the anaesthetist, in light of the recent changes in perioperative fluid management. It has become clear that the *liberal hydration* policy practised for years by most anaesthetists, has been based on flawed logic, and has been, to a large extent, inappropriate and even harmful to patients.[1] This makes the management of the renally challenged patient more complex – a clear approach is vital.

The focus of this review will be on *radiocontrast* as a cause of nephrotoxicity. With advances in medical science, we have seen an increased usage of invasive radiology techniques for both diagnostic and therapeutic procedures. The radiocontrast media used in these procedures may, however, invoke a typically reversible form of acute renal failure. This review aims to highlight a few of the relevant, and as yet, not fully resolved issues.

TYPES OF RADIOCONTRAST AGENT[2,3]

Iodinated radiocontrast agents are typically described in terms of *structure* (ionic and non-ionic monomers or dimers) and *osmolality*.

First generation agents

These are *ionic monomers* (benzene ring + 3 I_2 atoms). These agents have an osmolality of ~ 1400 - 1800 mosmol/kg and are therefore hyperosmolar with respect to plasma (~ 290 mosmol/kg).

Second generation agents e.g. Iohexol (Omnipaque®), Iopamidol (Jopamiron®)

These are *nonionic monomers* with an osmolality < than that of the 1st generation agents (500 - 850 mosmol/kg). Although these agents are termed '*low osmolality' agents*, it must be noted that they are still hyperosmolar with respect to plasma.

Until recently, all available *nonionic* agents were such 'low osmolality' agents. In addition, there is an ionic low osmolar contrast agent (*ioxaglate – Hexabrix®*). Although *ionic*, this intermediate agent has a low osmolality. This is because the I_2-containing organic molecule, being a dimer, is twice as large as the other molecules in the ionic group. There are, therefore, half the number of osmotically active particles per gram of I_2 in solution.[27]

The newest nonionic contrast agents are *dimers* (two benzene rings joined together as a single molecule) with an even lower osmolality. *Iodixanol (Visipaque®)*, the first such agent, is iso-osmolal (~ 290 mosmol/kg) with respect to plasma.

Note, therefore, that the 'iso-osmolal agents' have a lower osmolality than so called 'low osmolal' second generation drugs. The nephrotoxic properties of these agents appear to vary, with low- and iso-osmolal agents being associated with a relatively decreased incidence of renal injury among high-risk patients.[2]

HIGHLIGHTS

1. Why the fuss?
Perioperative renal failure in general has an incidence of 0.1 - 50% and a mortality of ~ 50% – a statistic which has not changed in 50 years.

2. Why the kidney?
The kidney has a unique anatomical and physiological make-up, which renders it particularly vulnerable to insult:

a) *Cortico-medullary gradient*: The cortex gets 90% of the blood flow, but is responsible for only 10% of the metabolic work. The medulla gets only 10% of the renal blood flow (RBF), but is responsible for 90% of the metabolic work. (Na^+/ K^+ ATPase dependant solute resorbtion). – i.e. high O2 requirements of active Na^+ transport and counter-current mechanism.

b) This metabolically active medulla operates in a chronically 'hypoxic environment' with medullary $Pa0_2$ ~ 10-20mmHg cf Cortical $Pa0_2$ ~ 50mmHg. Medullary blood supply is also viscous due to osmotic removal of water.

c) The renal medullary vascular bed, the vasa recta, is composed of long vessels of small diameter. Blood flow is facilitated by maintenance of low viscosity. The medullary thick ascending loop (mTAL) cells are therefore particularly at risk in the face of hypotension or decreased RBF.

PATHOGENESIS

The mechanism of contrast-induced *acute tubular* necrosis is not fully understood. Animal research supports two major theories:

1. Renal vasoconstriction: Possibly mediated by decreased nitric oxide, increased or decreased endothelin, and/or increased adenosine – resulting in medullary hypoxaemia.

2. Direct contrast-mediated cytotoxicity.

Additional contributors may include: rheologic alterations, activation of the tubuloglomerular feedback mechanism, regional hypoxia, and production of reactive oxygen species.

1. Renal vasoconstriction

Renal vasoconstriction occurs commonly and is believed to be due to a combination of contrast-induced release of vaso-constrictors like *endothelin* and *adenosine* on the one hand, and a decrease in endogenous vasodilators like *nitric oxide* and *prostaglandins* on the other. Preliminary human studies suggest, however, that the role played by endothelin may not be significant. Wang *et al*[4] showed that endothelin receptor antagonists failed to prevent contrast-induced renal failure.

Weisberg[5] showed that renal vasoconstriction alone correlates poorly with subsequent rise in plasma creatinine. Reduced medullary flow may, however, still be of primary importance. The vasoconstrictor *iotholamate* decreased medullary blood flow in rats but did not produce renal failure until it was given together with *blockers of nitric oxide and prostaglandin*.[6]

Patients with diabetes mellitus and heart failure have an increased risk of developing contrast-induced renal failure. This is possibly

due to impaired *nitric oxide* generation. This reduction in medullary blood flow may be compounded by an increased *blood viscosity*, as is seen with contrast media, in particular high- and low-osmolal preparations. As mentioned previously, the medullary vasa recta are long, thin blood vessels and flow through them depends on maintenance of a low viscosity. Increased viscosity may also enhance tubular interstitial pressure, which further reduces medullary blood flow.

2. Direct cytotoxicity
The second theory implicates the ability of the contrast agent to cause tubular injury - either directly, or via release of *oxygen free radicals*. Antioxidant activity may explain the apparent benefit of acetylcysteine and some animal models suggest that decreased activity of protective antioxidant enzymes may explain the enhanced risk with hypovolaemia.

Both of these mechanisms probably play a role. In a study by Katholi *et al*[7], for example, administration of a *nonionic, low-osmolality* contrast agent led to an 18% decrease in creatinine clearance and increased adenosine excretion. Concurrent use of theophylline, an adenosine receptor antagonist, prevented the fall in creatinine clearance. In comparison, an *ionic high-osmolality contrast* agent produced a 42% reduction in creatinine clearance that was only partially corrected by theophylline and that was associated with a more prolonged increase in adenosine excretion, suggesting concurrent tubular injury.

INCIDENCE
Reported incidence varies widely (0% - 50%) due to differences in: risk factors present (primarily underlying renal disease), the definition of contrast-induced nephropathy, the amount and type of administered agent, statistical analysis technique (prospective vs retrospective) and type of radiological procedure. In addition, most studies do not reliably exclude other causes of acute renal failure (e.g. arteriography induced atheroemboli).

Radiocontrast studies frequently result in a small rise in the plasma [creatinine] (averaging 0.2 mg/dl [18 µmol/l]). A more significant rise of > 50 % above baseline or of > 1 mg/dl (88 µmol/l) is generally only seen in the presence of severe or multiple risk factors.

RISK FACTORS
- Pre-existing renal insufficiency [plasma creatinine] > 1.5 mg/dl (132 µmol/l) or a GFR < 60 ml/min per 1.73 m^2 (not usually measured clinically).
- Diabetic nephropathy.
- Any cause of reduced renal perfusion e.g. advanced heart failure or hypovolaemia.
- High total dose of contrast agent (or multiple contrast studies within a 72 hour period). Some studies show that low doses of contrast (variably defined as < than 70 ml, < 125 ml, or < 5 ml/kg [to a maximum of 300 ml], divided by the plasma [creatinine]) are less likely to cause renal dysfunction. Manske[8] showed, however, that diabetics with [plasma creatinine] > 5 mg/dl (440 µmol/l) may be at risk from as little as 20 - 30 ml of contrast.
- Percutaneous coronary intervention: (contrast, atheroemboli, myocardial ischaemi-related hypoperfusion).
- Multiple myeloma: is associated with less than 1.5 % incidence of renal failure if a modern contrast agent is used. Contributing factors include: *Volume depletion* (promotes the intratubular precipitation of filtered light chains) and a possible *interaction between light chains and the contrast agent.*

CLINICAL PRESENTATION
Radiocontrast induced renal failure is usually mild, transient and nonoliguric. It begins within 12 - 24 hours of contrast administration and usually recovers within 3 - 5 days. Occasional patients may develop more significant renal dysfunction with creatinine peaks > 5 mg/dl (440 µmol/l). This usually occurs if baseline plasma creatinine > 4 mg/dl (352 µmol/l), and may require *dialysis*. *Persistent renal failure* has been described and occurs primarily in patients with pre-existing advanced underlying disease, particularly in diabetics.

McCullough *et al*[9] reviewed more than 1800 consecutive patients who underwent coronary intervention with contrast. The overall incidence of acute renal failure was 14.4% and 0.8% of these required dialysis. The need for dialysis significantly increased both in-hospital mortality, and two year survival was only 19%.

DIAGNOSIS
The diagnosis of radiocontrast nephropathy is based on the characteristic rise in plasma creatinine concentration, beginning within the first 12 - 24 hours. In the differential diagnosis be sure to consider conditions like, *ischaemic acute tubular necrosis and acute interstitial nephritis*, (especially if an additional insult like sepsis, hypotension, or medication exposure was present) and *renal atheroemboli*.

Any diffusely atherosclerotic patient undergoing arteriography is at risk of *renal atheroemboli* and the following features help distinguish this event from *contrast nephropathy*:

- The presence of other embolic lesions (as on the toes) or livedo reticularis.
- Transient eosinophilia and hypocomplementaemia.
- Delayed onset renal failure (days to weeks post-procedure).
- Protracted course with frequently little or no recovery of renal function.

PREVENTION OF RADIOCONTRAST MEDIA-INDUCED ACUTE RENAL FAILURE[3]
There is no specific treatment for contrast-induced acute renal failure. If it develops it should be managed as you would any cause of *acute tubular necrosis*, focusing on fluid maintenance and electrolyte balance. The best treatment of the nephropathy is therefore *prevention*.

Suggested methods for reducing the incidence of this entity include:

1. Where at all clinically possible, it may be worth considering *alternative diagnostic modalities* such as: *ultrasonography, magnetic resonance imaging with gadolinium*, or *CT scanning without radiocontrast agents* – particularly in high risk patients.
2. The use of *low or iso-osmolal, nonionic* contrast agents wherever possible.
3. Limit both the *total dose* and the *number of doses* administered in a 48 - 72 hr period.
4. CO_2 can be used as an alternative contrast agent in certain high risk patients.
5. Limiting contributory risk factors like: *hypovolaemia*, *NSAIDs,* and *certain antibiotics*.
6. Many specific prevention strategies have been investigated. These include intravenous saline, sodium bicarbonate, acetylcysteine (antioxidant), prophylactic haemofiltration/haemodialysis, aminophylline, vasodilators, diuretics, statins, ascorbic acid, etc.

Pannu *et al*[10] note that most of the clinical trials looking at these interventions have used small, transient elevations in the plasma creatinine concentration as an end point (e.g.≥ 0.5 mg/dL [44.2 mmol/L] or ≥ 25 to 50% > baseline). These authors questioned the significance of these small increases, but several studies since suggest that contrast-induced nephropathy defined in this manner, is in fact associated with significant in-hospital and long-term mortality.

Type of contrast agent
The risk of contrast nephropathy appears to be a function of both the agent *structure* (ionic vs non-ionic compounds) and the agent *osmolality* relative to plasma ('hyperosmolal': [1400 to 1800 mosmol/kg]; 'low osmolal': [500-850 mosmol/kg] or 'iso-osmolal': [~ 290 mosmol/kg]). The incidence appears to be lower with agents that are non-ionic and agents that are non-hyperosmolar.

Most current radiological procedures requiring intravenous contrast use the non-ionic, low osmolal agents due to low cost, increased patient tolerability, and decreased hypersensitivity reactions.

There are few direct comparisons between various agents, however, and many questions remain unanswered. The data suggests:

- The primary benefit of nonionic contrast agents, whether low or iso-osmolal, is seen in high-risk patients (e.g. plasma [creatinine] ≥1.5 mg/dl (132 mmol/l) or a glomerular filtration rate (GFR) of < 60 ml/min per 1.73 m^2), particularly if they are diabetic.
- *Iodixanol* is at present the only non-ionic, *iso-osmolal* agent available. It appears to be superior to some of the low osmolal agents in its ability to reduce the risk of contrast nephropathy in high-risk patients (e.g. diabetics with renal insufficiency). It is, however, expensive and further work is required to establish the extent and consistency of this perceived benefit.

Carbon dioxide has been used successfully as an alternative contrast agent (alone or in combination with small doses of iodinated contrast) in high risk patients. It is, however, *neurotoxic* and should not be used for cerebrovascular imaging. All access to the cerebral circulation should be limited (e.g. right to left intra-cardiac shunts) and its use should therefore be limited to imaging below the diaphragm.

CONTRAST-ENHANCED MRI

Unlike the *iodinated contrast agents* used in CT imaging and angiography, those used in MR imaging are *chelates of gadolinium*, which have been found to be less nephrotoxic, if used in small doses. Some have looked at these *paramagnetic* contrast agents as an alternative in digital subtraction angiography or interventional procedures, particularly in patients with renal insufficiency or iodinated contrast allergy. Emerging data suggests that if given in doses > 0.3 mmol.kg, nephrotoxicity may occur. These agents do, however, appear to be safer and may be preferable in high risk patients requiring vascular imaging. At the recommended dose of < 0.3 mmol.kg, however, diagnostic image quality is diminished and the modality is not supported by the radiological fraternity.

SPECIFIC STRATEGIES

1. Hydration

Optimal hydration is a vital component of any renal protection strategy. It would appear that intravenous hydration is superiour to oral hydration. The optimal fluid choice, infusion rate and volume are unclear. Investigated solutions include *isotonic normal saline*; *half normal saline* and *isotonic sodium bicarbonate*.

Fluid selection and rate of administration must take into consideration: a) Recent changes in overall perioperative *hydration policies*; b) the patient's ability to tolerate a *fluid load* (e.g. may precipitate failure in individuals with reduced left ventricular function); c) the ability to tolerate *alkalinisation*; and d) the degree of underlying risk for nephropathy.

Mueller *et al* [11] (2002) enrolled 1620 patients in a prospective randomised controlled trial, and compared the effects of a 1 ml.kg.hr infusion of either *isotonic normal saline* or *half normal saline* from the morning of the procedure. The incidence of 'contrast nephropathy' (defined as an increased [creatinine] of 0.5 mg/dl (44 mol/l) within 48 hours) was 0.7% in the isotonic saline group and 2% in the half normal saline group.

Alkalinisation may protect against free radical injury. For this reason Merten *et al* [12] (2004) did an isotonic normal saline (154 meq/l) vs sodium bicarbonate comparison. These solutions were administered as a bolus of 3 ml/kg/hr over the one hour pre-contrast, followed by a 1 ml/kg/hr infusion for six hours post contrast. This study showed marked benefit in those given sodium bicarbonate, but study weaknesses necessitate the need for further work to fully define its role.

An increasing number of patients receive contrast as outpatients. This has prompted a few researchers to look at the effectiveness of *oral hydration* or *salt loading*, and also the benefits of an *outpatient hydration protocol*. The safety and efficacy of these modalities for the prevention of contrast nephropathy is uncertain, and intravenous hydration remains the route of choice.

2. Acetylcysteine (Solmucol®)

This agent is a thiol compound with antioxidant and vasodilatory properties. A theoretical mechanism of benefit in the prevention of contrast nephropathy therefore, would include minimising contrast induced *vasoconstriction* and oxygen *free radical* generation.

Many prospective trials have looked at acetylcysteine as a renoprotective agent, and the results are markedly inconsistent. Reasons for this probably include: varying *definitions* of contrast-induced acute renal failure, *varying degrees* of renal dysfunction and diabetes, *varying protocols* (type, dose and route of administration) of acetylcysteine, hydration and contrast usage, and varying types of *procedure* (e.g. contrast CT, cardiac catheterisation, or peripheral angiography).

Several *meta-analyses* have been conducted and the trend is suggestive of benefit.

Nallamothu[13] in 2004 looked at data from twenty randomised trials (2195 patients). Acetylcysteine was associated with a 27% reduction in the risk of developing contrast-induced nephropathy (risk ratio 0.73, 95% CI 0.52 to 1.0). An analysis limited to the 11 placebo-controlled double-blind trials yielded a risk ratio of 0.56 (95% CI 0.33 to 0.95).

Dosing

The most commonly studied dose regimen for acetylcysteine prophylaxis is 600mg orally twice daily. Nallamothu evaluated this regimen in a subgroup analysis of twelve studies and reported a summary risk ratio of 0.73 (95% CI 0.46 to 1.2). However, two studies (Briguri *et al* [14] in 2004 and Marenzi *et al* [15] in 2006) comparing 600 mg and 1200 mg twice daily, suggested slightly better outcomes with the higher dose. So, if it is to be used, acetylcysteine can be administered to patients at risk, at a dose of 600 - 1200 mg orally twice daily on the day before, and on the day of the procedure.

Where oral premedication is not possible or, for example, in emergency coronary angiography, *intravenous acetylcysteine* has been considered. Once again results are conflicting and benefit uncertain.

Webb *et al* [16] in 2004 looked at 487 patients with a mean baseline plasma creatinine of 1.6 mg/dl (140 μmol/l) in a placebo controlled trial. All the patients received isotonic saline (200 ml before the procedure and 1.5 ml/kg.hr for 6 hours after) and found no benefit to therapy with *500 mg of intravenous acetylcysteine* just prior to the procedure.

A trial by Baker *et al* [17] (2003), on the other hand, did demonstrate benefit. He looked at 80 patients with a mean baseline creatinine of 1.8 mg/dl (160 μmol/L). *Intravenous acetylcysteine* (150 mg/kg pre-procedure and 50 mg/kg over four hours, post-procedure) was compared with isotonic saline (1 ml/kg.hr for 12 hours pre- and post-contrast). Fewer patients (5%) in the acetylcysteine group developed acute renal failure, as compared to 20% in the control group. However, at the high doses used, 7% developed *anaphylactoid reactions*.

On the basis of conflicting data and a documented risk of *anaphylactoid reactions*, Rudnick *et al* [3], do not advocate the routine use of intravenous acetylcysteine for the prevention of contrast nephropathy.

3. Prophylactic haemofiltration and haemodialysis

This has been examined, based on the theory that removal of the inciting compound from the circulation might prevent contrast-induced acute renal failure.

Marenzi *et al* [18] (2003) compared *haemofiltration* with *intravenous saline* in 114 high risk patients. These patients had chronic renal failure (mean [creatinine] 3 mg/dl [265 μmol/l]) and required a coronary intervention. They were randomly assigned to *saline hydration* (1 ml/kg.hr) or *haemofiltration* (1000 ml/hour fluid replacement rate), begun 4 - 8 hours prior to the procedure, resumed after the procedure and continued for 18 - 24 hours.

Approximately 250 ml of *nonionic, low-osmolality contrast agent* was used in each group.

The haemofiltration group showed less chance of [creatinine] rising more than 25% above baseline, less chance of requiring dialysis, and lower in-hospital and one year mortalities. Study flaws make interpretation of these results (and those of similar studies) difficult, however, and taken together with the fact that it is an expensive and cumbersome modality, its routine clinical application is not warranted.

Prophylactic *haemodialysis* has been advocated for both the removal of contrast and for the prevention of volume overload. Studies have not shown benefit and it too can not be recommended in routine clinical practice.

4. Aminophylline
Adenosine is a well known coronary and peripheral vasodilator. Renal work has, however, shown it to vasodilate only isolated rings of renal vasculature and to generally result in *renal vasoconstriction*. Aminophylline inhibits the adenosine receptor, thereby preventing vasoconstriction. Many trials have looked at its potential renoprotective benefit, but results are conflicting. Bagshaw[19] (2005) did a meta-analysis of nine controlled trials in which he compared 585 patients who received *theophylline*, with controls. The theophylline group showed a marginal benefit and patients studied were at relatively low risk (only one case required dialysis). In contrast, concurrent administration of an adenosine agonist like the antiplatelet agent *dipyridamole*, may increase contrast toxicity.[7]

As mentioned earlier, Katholi *et al*[7], showed that theophylline prevented a fall in measured creatinine clearance post administration of a nonionic, low-osmolality contrast agent. The protective effect was only partial when an ionic high-osmolality contrast agent was used.

5. Dilators
It is unclear if pharmacologic inhibition of renal vasoconstriction will protect high risk patients from developing renal failure. The acute reduction in GFR induced by contrast agents may be theoretically minimised or prevented in some patients, by the use of vasodilators. Various agents have been proposed as renal vasodilators but there is little evidence to support their routine use. Agents include:

a. Dopamine
Dopamine was reported in the 1970s to increase RBF at low doses (3 μg.kg.min) by mediating DA1 induced- vasodilatation. Subsequent evidence suggests that renal effects of dopamine are more complex and may even be harmful to the high risk kidney. Inceased RBF may be due to the inotropic related increase in cardiac output, and the diuresis is probably due to a direct tubular action.

Numerous studies now attest to the potential harmful effects of dopamine (arrhythmias; myocardial, peripheral vascular and gut ischaemia; pulmonary hypertension; impaired hypoxic ventilatory response; decreased gastric motility; increased metabolic rate and weight loss; endocrine and immune dysfunction) and its routine use is not warranted.

b. Fenoldopam
This is a selective DA1 agonist with vasodilating properties in renal, mesenteric, coronary and cerebral beds. It is claimed to be renoprotective due to its ability to increase RBF, urine output and Na^+ excretion, but its role in peri-operative renal protection is as yet undefined. Its main use remains the treatment of severe hypertension in the presence of renal failure, as it drops blood pressure rapidly and safely.

A prospective randomised trial ('CONTRAST')[20] assessed the effectiveness of *fenoldopam* in 315 chronic renal failure patients (half diabetic) undergoing a cardiovascular procedure. All patients also received half normal saline, and contrast nephropathy was defined as an increase in serum creatinine of ≥ 25 percent above baseline in the first four days. There was no reduction in the incidence of contrast nephropathy in the fenoldopam group (34 versus 30% with placebo). It has been proposed that direct intrarenal administration may be more beneficial.[21]

c. Nitroglycerine
This agent has no specific renoprotective action but maintains RBF and decreases renal vascular resistance in contrast to sodium nitroprusside (SNP), which decreases renal blood flow (RBF) and maintains renal vascular resistance (RVR).

d. Endothelin antagonism
The possible importance of endothelin-induced renal vasoconstriction led to the evaluation of a *nonselective endothelin receptor antagonist* in a multicentre, double-blind randomised trial of high-risk patients undergoing coronary angiography.[4] Compared with those assigned to placebo, a significantly higher percentage of patients who received active therapy sustained contrast nephropathy (56 versus 29%); this observation raises the possibility that endothelin may actually provide an intrinsic protective effect rather than contributing to the development of acute renal failure. Alternatively, selective endothelin receptor antagonists may be required to demonstrate prophylactic value in this setting.

e. ACE-inhibitors (ACEIs)
ACEIs are theoretically beneficial via the blocking of renin angiotensin system (RAS)-induced vasoconstriction, but benefit remains unproven. Remember also their ability to precipitate acute renal failure (ARF) in patients with bilateral renal artery stenosis, as they inhibit angiotensin-mediated efferent artery vasoconstriction (necessary to maintain GFR in these patients).

f. Alpha-agonists
Clonidine showed animal benefit in the 1980s.

g. Beta-blockers
They are theoretically beneficial via their ability to block renin release but benefit remains unproven.

b. Calcium-channel blockers
Both ischaemic and toxic ARF show an accumulation of intracellular Ca^{++} which blocks ATP production and cellular regeneration. This prompted investigation of the renoprotective abilities of Ca^{++} channel blockers. Animal studies show some protection with verapamil and nifedipine, but follow up clinical studies have been inconsistent. Colsen (AandA 1992) demonstrated benefit of nicardipine in humans. These drugs have the potential to worsen renal function in unstable patients as cardiac depression and vasodilation may further decrease RBF and GFR.

i. Prostaglandin E2 (PGE2)
PGE_2 is a renal vasodilator (opposes action of TXA_2) and therefore improves RBF. It may also decrease mTAL active transport and thus decreases energy expenditure. *Note*: Angiotensin causes renal vasoconstriction BUT also stimulates PGE_2 production to maintain balance. NSAIDs block this vasodilatation and unmask angiotensin mediated vasoconstriction.

6. Diuretics
The theoretical renoprotective properties of diuretics include:

- Free radical scavenging.
- Decreased oxygen consumption of mTAL cells.
- Tubular effects: diuresis, high tubular flow, prevention of obstruction, prevention of tubular swelling, inhibition of tubulo-glomerulo feedback; therefore decreases GFR.
- Haemodynamic effects: decreases renin release; direct arterial smooth muscle relaxation and increased PG synthesis, which results in increased RBF, decreased RVR and the re-establishment of the cortico-medullary gradient.

a. Mannitol
Work in the early 1980s suggested a potential role, but subsequent trials have confirmed both no benefit and a significant complication rate.

b. Furosemide
Animal experiments show a significant increase in GFR in

ischaemic ARF but not in toxic ARF. Clinical evidence shows increased urine output, but no difference in mortality or in the need for dialysis.

Diuretics may increase urine output in some cases of renal impairment, but it is not clear whether conversion of oliguric renal failure to non-oliguric renal failure improves outcome or not. Anderson *et al* (1977) converted oliguric ARF to non-oliguric ARF with high dose furosemide (10 mg/kg) and showed lower $FENa^+$ despite similar urea and creatinine. They also demonstrated fewer complications, shorter hospital stay and lower mortality. Brown *et al* (1981 and 1991) and numerous other studies dispute the proposal that maintenance of a high urine output has any influence on outcome.

Solomon *et al* [22] (1994) took 78 patients with stable chronic renal failure (mean plasma [creatinine] = 2.1 mg/dL [186 mmol/L]) about to undergo coronary angiography and randomly assigned them to one of three regimens:

1. Half isotonic *(0.45 percent) saline* at a rate of 1 ml/kg per hour for 12 hours before and 12 hours post angiogram.
2. Half isotonic saline plus 25 g of *mannitol* infused intravenously over the hour prior to the procedure.
3. Half isotonic saline plus 80 mg of *furosemide* infused intravenously over the 30 minutes prior to angiography.

The incidence of ARF (defined as an increase in plasma [creatinine] 0.5 mg/dl (44 mmol/l) was lowest in group 1 (saline alone); mannitol conferred no extra benefit and there was a suggestion that furosemide slightly increased the incidence. Why this might occur is not known, since volume depletion due to the diuresis was not seen. Diabetics were at greater risk, but the incidence of renal dysfunction did not differ between ionic and nonionic contrast media.

c. Atrial natiuretic peptide (ANP)

Gorfinkel *et al* (1970s) showed that RBF was better maintained in cardiogenic shock than in haemorrhagic shock. They showed that left atrial pressure was maintained in cardiogenic shock, and this attested to the importance of atrial distension, and subsequent release of ANF and its active peptides API and APII. These substances have tubular and vascular actions, and the synthetic analogues, *Anaritide*® and *Ularitide*® have shown clinical promise.

Atrial natriuretic peptide (Anaritide®) has shown benefit in animal models of contrast nephropathy.[24] Kurnick *et al* however, observed no benefit in a multicentre, prospective, double-blind, placebo-controlled randomised trial.[25] In this study, 247 patients (with a plasma [creatinine] > than 1.8 mg/dl [159 mmol/l] or between 1.5 and 1.8 mg/dl [133 to 159 mmol/l]) undergoing radiocontrast administration were randomly assigned to placebo or to one of three intravenous doses of A*naritide*® given 30 minutes before and continued for 30 minutes after the procedure. Compared to placebo, active therapy at any dose failed to reduce the incidence of nephropathy in all patient groups, including those with diabetes.

Weisberg *et al* [23] (1994) took 50 patients with moderate chronic renal failure (mean plasma [creatinine] of 2.5 mg/dL [220 mmol/L]) about to undergo coronary angiography, and randomly assigned them to receive either saline or one of three renal vasodilator/diuretic drugs: dopamine @ 2 μg/kg.min; mannitol (15 g.dl in half isotonic saline at 100 ml.hr); or atrial natriuretic peptide.

Contrast toxicity was defined as an increase in the plasma [creatinine] of 25%. The saline group showed a 40% incidence of renal dysfunction in both diabetics and non-diabetics, as compared to the 75 - 83% incidence seen in all 3 of the drug groups. This increased incidence seen with the vasodilator/diuretic agents was, however, confined to diabetic patients. In fact no cases were seen in the non-diabetic subgroup, suggesting a possible benefit in this group.

7. Statins

Based on the documented ability of *statins* to improve endothelial function, reduce arterial stiffness (via improved endothelin-mediated vasodilatation), and reduce inflammation and oxidative stress, Khanal *et al* [25] (2005) examined their potential benefit in contrast nephropathy. A retrospective study of 28,871 patients undergoing percutaneous coronary interventions found that the incidence of contrast nephropathy (increase in serum creatinine of 0.5 mg/dl [44 μmol/l] or greater) was 4.4% among statin users and 5.9%, in non-users. Rudnick *et al*[2] point out, however, that fewer than 4% of patients in either group received pre-procedure *n-acetylcysteine*; the proportion receiving pre-procedure *hydration* was not reported; and that the influence of other non-measured variables on the results could not be ascertained. On this basis they do not recommend routine statin use.

8. Ascorbic acid

Ascorbic acid has been seen to diminish renal damage in experimental models of ischaemic or toxic injury. On this basis, Spargias *et al*[26] (2004) examined its potential benefit in contrast nephropathy, in a randomised, placebo-controlled study of 231 patients with plasma [creatinine] 1.2 mg/dl (106 μmol/L) who underwent coronary angiography with or without percutaneous intervention. Patients in the active therapy arm received 3 g of ascorbic acid at least 2 hours pre-procedure, and 2 g on the night and morning following the procedure. Contrast nephropathy (an increase in plasma creatinine by 0.5 mg/dl [44 μmol/L] or by 25% during days two to five after the procedure) was 9% in the active therapy group and 20% in the placebo group. Further work is required to define the role of ascorbic acid.

9. Growth factors (insulin-like growth factor and epidermal growth factor)

These factors have shown a promising ability, in animal studies, to enhance renal cell regeneration and growth, and thus hasten recovery from acute renal failure.

10. Future agents

Modalilities may include agents like iNOS (inducible nitric oxide synthetase); and ANTI-ICAM (cellular adhesion molecules).

SUMMARY AND RECOMMENDATIONS

Optimal prophylaxis for contrast nephropathy remains uncertain. Patients with near-normal renal function are at little risk and few precautions are necessary other than avoidance of volume depletion.

Patients at increased risk of nephropathy are defined by Rudnick et al as those with a plasma creatinine 1.5 mg/dl (132 mmol/L) or an estimated glomerular filtration rate < 60 ml/1.73 m^2, particularly in patients with diabetes. They recommend:

- Alternative (non-contrast) diagnostic modalities where possible (ultrasound; MRI; CT scan).
- Avoid high osmolal agents (1400 to 1800 mosmol/kg) – Grade 1A.
- Iso-osmolal agents (~ 290 mosmol/kg) are preferable to low osmolal agents (500 to 850 mosmol/kg) – Grade 2B.
- Use lower doses of contrast and avoid repetitive, closely spaced studies (e.g. < 48 hrs apart).
- Avoid volume depletion and nonsteroidal anti-inflammatory drugs.
- If there are no contraindications to volume expansion, give isotonic intravenous fluids prior to and continued for several hours after contrast administration – Grade 1B.
- The optimal type of fluid and timing of administration are not well established. However, since isotonic saline has been the hydration regimen used in the majority of studies showing benefit, it remains the fluid of choice – Grade 2B. *(See suggested regimen)*
- Acetylcysteine at a dose of 600 - 1200 mg orally twice daily, administered the day before and the day of the procedure. Data is conflicting, but it is worth using based on its potential for benefit, low toxicity and cost – Grade 2B.

  The intravenous route is not recommended based upon the lack of convincing evidence of benefit, and the potential risk of anaphylactoid reactions – Grade 2B.

A suggested fluid regimen

Isotonic saline at a rate of 1 ml/kg per hour, begun at least two and preferably 6 - 12 hours prior to the procedure, and continuing for 6 - 12 hours after contrast administration. The duration of administration of fluid should be increased proportionately with more severe degrees of renal impairment.

Data comparing isotonic bicarbonate to isotonic saline is limited. The bicarbonate regimen may be preferable if there is not sufficient time for isotonic saline hydration prior to the procedure. A suggested regimen is:

A bolus of 3 ml/kg of isotonic bicarbonate over the 1 hour pre-procedure, and continued at a rate of 1 ml/kg for 6 hours post-procedure. This solution can be prepared by adding 150 meq of sodium bicarbonate (three 50 ml ampoules of 1 meq/mL sodium bicarbonate) to 850 mL of 5 % dextrose in water.

- Diuretics should be reserved for patients with volume overload. Mannitol should specifically be avoided – Grade 2B.

- Haemofiltration/haemodialysis are not recommended – Grade 2B.

Fluid considerations

Fluid volume[1]

Fluid therapy is clearly a mainstay of renal protection and yet the topic itself is highly controversial. Brandstrup et al in 2006, reviewed the evidence guiding 'standard' perioperative fluid therapy and came to the following conclusions:

- The evaporative loss from the abdominal cavity is highly overestimated.
- The non-anatomical '3rd space' loss is based on flawed methodology and is probably non-existent.
- The fluid volume accumulated in traumatised tissue is probably very small.
- The volume preloading of neuraxial blockade is not effective and may cause postoperative fluid overload.

Many trials show that so called 'restricted fluid strategies' are associated with better outcome than the traditional liberal hydration protocols. Brandstrup states that in view of their conclusions reached, these strategies are not evidence-based at all, and that 'restricted' fluid administration is in fact not 'restricted' at all, but rather replaces only the small amount of fluid lost during surgery, thereby avoiding the overload resulting commonly from overestimation of perioperative losses.

Fluid type[28]

The fluid most commonly used in the renoprotective trials showing benefit, is 0.9% normal saline. Considerations include:

- 'Normal' saline is not an ideal crystalloid solution. It is significantly hypertonic (osmolality = 308 mosmol.l) and contains a very high content of chloride (154 mmol.l)
- It has been shown that saline infusions of as little as 2 litres, result in significant 'hyperchloraemic metabolic acidosis'.
- There is also evidence that chloride loading may impair renal function (dose-dependant vasoconstriction and decreased GFR) and may interfere with coagulation.
- The significance of this acidosis is unclear, but volunteer studies display numerous adverse effects associated with chloride loading. No human data exists to show that this decreases survival.

These findings may mean that normal saline is not the ideal fluid for prevention of nephropathy. None of the available crystalloids, however, approximate the electrolyte content of plasma. This includes Ringer's lactate (Cl^- =115mmol.l; Na+ = 131mmol.l and osmolarity = 273mosmol.l; measured osmolality due to incomplete ionisation of lactate salts = 255mosmol.l).

Perhaps the future will see better results with a more balanced salt solution being used to maintain hydration.

CONCLUSION

Radiocontrast interventions are on the increase and patients run the risk of developing Contrast-Induced Renal Failure. It is the anaesthetist's responsibility to be aware of the entity and to make every effort to prevent it. The low risk patient may require little other than standard haemodynamic support, but the high risk patient may benefit from a reno-protective strategy. This lrequires a team effort involving careful use of *contrast media*, and the provision of evidence- based prophylaxis like *normal saline hydration* and *acetylcysteine*. It is the anaesthetist's responsibility also, to be aware of the controversies surrounding these interventions and to remain updated on new trends. **SAJAA**

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